Skin Substitutes

An Overview of the Key Players in Wound Management

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ABSTRACT

In a relatively short timespan, a wealth of new skin substitutes made of synthetic and biologically derived materials have arisen for the purpose of wound healing of various etiologies. This review article focuses on providing an overview of skin substitutes including their indications, contraindications, benefits, and limitations. The result of this overview was an appreciation of the vast array of options available for clinicians, many of which did not exist a short time ago. Yet, despite the rapid expansion this field has undergone, no ideal skin substitute is currently available. More research in the field of skin substitutes and wound healing is required not only for the development of new products made of increasingly complex biomolecular material, but also to compare the existing skin substitutes.
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A thorough understanding of wound management could provide superior results for the patient in terms of healing time, comfort, cosmetics, and costs. Wound management encompasses a gambit of options available for maximizing results, including a growing array of dressings, topical therapies, appropriate infection control, pressure offloading, medical management of systemic diseases, and skin substitutes. This review will focus on the latter, skin substitutes. When choosing the appropriate skin substitute, categorizing the wound as acute or chronic provides physicians with the framework to choose the most appropriate product (Figure 1).

Acute wounds are commonly encountered and in fact often created during dermatological procedures. More than 25 million minor surgical procedures under aseptic conditions occur yearly and the number continues to grow within the specialty.[1] Chronic wounds, defined as a break in the skin for greater than six weeks, or frequently recurring wounds, present their own unique challenges and represent a major burden on the healthcare system.[2] Wound healing can be broken down into four sequential, but overlapping phases including hemostatic, inflammatory, proliferative, and tissue remodeling phases.[3] Chronic wounds are often the result of an uncoordinated and perpetuating inflammatory response. The chronic wound environment thus includes excess proteases, increased cell senescence, increased bacterial bioburden, local pH disturbances, and hypoxia.[4,5]

Maintaining an environment conducive to repair involves elimination of necrotic tissue through debridement, control of bacterial loads, and management of wound exudates. It also requires maintaining a moist wound surface with open wound edges while insulating the wound.[6,7] Dressings are an integral component of wound management. Dressings thwart contamination from the local environment, absorb exudate from the wound bed, and maintain a moist wound environment.

Synthetic occlusive dressings, however, despite ongoing advancements, are not always able to correct the complex factors contributing to certain wounds.[8–11] Therefore, in more recent years, bioengineered and allograft-derived skin substitutes have been developed.[12] Skin substitutes can be categorized based on their origin into xenografts, synthetic grafts, allogeneic grafts, and autologous grafts. The ideal skin substitute should be durable, completely autologous, endothelialized, and contain adnexal structures and adult stem cells.[12] Such an ideal substitute is yet to exist. Skin substitutes will not provide immediate or permanent coverage for chronic wounds. Rather, they are used as an adjunct to the established tenets of wound care in order to increase the success rate of healing. Skin substitutes do so by providing matrix elements, growth factors, and paracrine signaling functions that favor a state of healing.[12–13] The following is an introductory overview of various substitutes and their indications.

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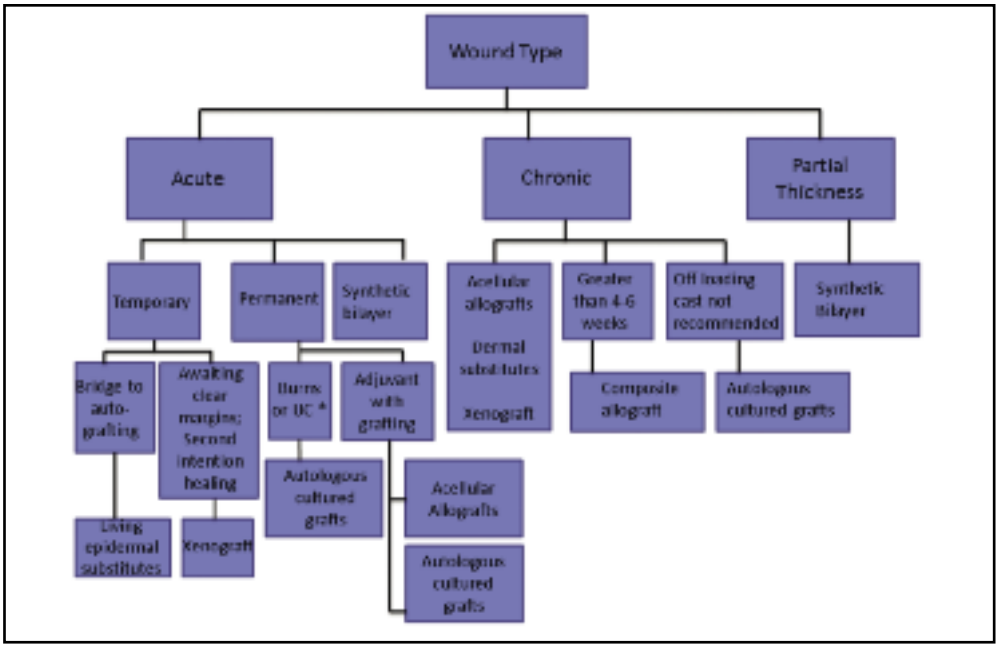

Figure 1. Skin substitutes; *UC = ulcerative colitis

XENOGRAFTS

Xenografts introduce exogenous collagen into the wound, which aids dermal regeneration. The exogenous collagen is believed to be chemotactic for macrophages and fibroblasts and provides a three-dimensional structure for the ingrowth of tissue.[14–15] Extracellular matrix material delivered to the wound bed helps reduce high levels of matrix metalloproteinases known to inhibit wound repair in chronic nonhealing wounds.[16] Examples include Permacol (Tissue Science Laboratories, Covington, Georgia), made of porcine dermis; Matriderm (Suwelack Skin and Health Care Ag, Billerbeck, Germany), composed of bovine collagen coated with elastin; and Oasis (Healthpoint, Fort Worth, Texas), derived from porcine instestinal submucosa.[17–18] These materials are used for acute burns, partial-thickness wounds, and full-thickness wounds, including chronic ulcers and traumatic injuries. Xenografts are absorbed as the wound heals, making them ideal for surgical wounds that are healing by secondary intention. They are also used as a temporary dressing while awaiting clear margins before definitive closure.[12] More studies are needed, but some have found xenografting to decrease pain. This can be partially attributed to the fact that they are applied during secondary intention healing covering vital structures.[12,19]

SYNTHETIC BILAYERS

Synthetic bilayer skin substitutes are composed of a porous matrix containing collagen and other extracellular matrix components. In addition, a layer of silicone functions as the epidermis and protects the wound from moisture loss and infection.[17] Examples include Biobrane (UDL Laboratories, Inc, Rockford, Illinois), AWBAT (Aubrey, Inc, Carlsbad, California), and Integra Dermal Regeneration Template (Integra Life Science Corp, Plainsboro, New Jersey). These synthetic bilayers are commonly used for partial-thickness wounds, full-thickness wounds, burns, and chronic ulcers and provide a scaffold for dermal regeneration and temporary wound coverage.[17,20] In superficial wounds, the membrane is placed in the wound and is replaced by host epithelium from the wound edge and adnexal structures. In deeper wounds, the membrane stimulates granulation tissue and facilitates autologous grafting. Problems with various synthetic bilayers include difficulty with initial wound adherence and fluid accumulation under the dressing, which can lead to seromas.[12,17,21]

ACELLULAR ALLOGRAFTS

As the name implies, acellular allografts are a category of skin substitutes that consist of decellularized human tissue. AlloDerm (Life Cell, Branchburg, New Jersey), Graftjacket (Wright Medical Technologies, Arlington, Tennessee), and GammaGraft (Promethean LifeSciences, Pittsburg, Pennsylvania) are a few examples and consist of cryopreserved human cadaveric dermis, which has been modified to remove donor cells and antigenic material in various ways, thus reducing the antigenic response. The remaining dermal structure serves as a template for growth of host fibroblasts and vascular tissue to aid in dermal regeneration.[17] These products are used for various wounds including autologous grafting and chronic ulcers, such as lower extremity diabetic ulcers. Negative aspects of these products include poor barrier function, short shelf-life, and possible disease transmission risks as residual deoxyribonucleic acid (DNA) remains in the tissue.[17,22,23]

ALLOGENEIC LIVING EPIDERMAL SUBSTITUTES

Traumatic skin wound management often necessitates a bridging therapy of allograft coverage to initially stabilize the wound bed prior to autografting. Traditionally, cadaveric allografts have been utilized. A newer technology consists of living human skin substitute, an example of which is Stratagraft (StrataGraft Corp, Madison, Wisconsin). Neonatal keratinocytes are used to generate a biologically functional, fully stratified epidermis that resides over a dermal component. Stratagraft has a barrier function similar to intact human skin and is pathogen-free, thereby reducing infection risks compared to cadaveric-based products.[17,24,25] Stratagraft is used for burn patients and other severe skin wounds and serves as a bridge before autografting as previously mentioned. No difference in autograft survival exists in wounds that are pretreated with Stratagraft compared to cadaver allograft.[24] Further, Stratagraft is well-tolerated and a sensitivity or immune response toward the keratinocyte progenitor cells is not mounted in patients with traumatic skin wounds.[17,26]

ALLOGENEIC DERMAL SUBSTITUTES

Dermagraft (Advanced BioHealing Inc, La Jolla, California) is a cell-based dermal substitute derived from newborn foreskin.[12] The allogeneic fibroblast cells from human foreskin are seeded onto a polyglactin mesh scaffold where they proliferate and secrete cytokines to create a metabolically active dermal substitute.[17] The cells and scaffold stimulate autologous tissue repair and are not meant to be permanently incorporated.[13] Rather, fibroblasts and extracellular matrix continue to secrete growth factors once placed into the wound. Dermagraft is most effective if the graft is metabolically active.[27] The product is cryopreserved, requiring the clinician to thaw the material.[17] Dermal substitutes are used for full-thickness diabetic foot ulcers, venous ulcers, fasciotomy wounds, and other chronic wounds.[17,28–30] Weekly application of Dermagraft resulted in the highest rate of healing in one study of diabetic foot ulcers.[28] Similar to other skin substitutes, Dermagraft must be used as an adjunct to the standard of care including debridement, pressure offloading, and moist wound healing to be fully effective in chronic wounds.[31] Dermagraft is relatively safe, but infection, cellulitis, and osteomyelitis have been reported.[31]

COMPOSITE ALLOGRAFTS

Composite allografts refer to material that resembles full-thickness human skin without the appendageal structures, vasculature, and rete ridges. They consist of a collagen scaffold with cultured fibroblasts and a layer of stratified human keratinocytes. Examples of composite allografts include Apligraft (Organogenesis, Inc, Canton, Massachusetts) and Orcel (Forticell Bioscience, Inc, New York, New York).[17] Apligraf is a composite allograft bilayer formed by a layer of bovine collagen gel with neonatal fibroblasts for its dermis. Its epidermal layer is composed of neonatal keratinocytes.[17,32] It provides growth factors from both epidermal cells and fibroblasts, which stimulate healing.[12,33] Apligraf is approved for venous ulcers greater than one month duration that have not adequately responded to conventional therapy and for diabetic foot ulcers lasting greater than three weeks.[17,34] Venous ulcers present for longer than six months responded significantly better than those that were less than six months old.[35] It can also be used in epidermolysis bullosa,[34,36] acute surgical defects,[37] and split-thickness graft donor sites.[38–40] Apligraft is cost effective as patients experience faster healing and decreased complications.[17,35,41–44]

AUTOLOGOUS CULTURED SKIN GRAFTS

In 1975, a novel way of culturing human keratinocytes allowed for rapid epidermal fold expansion, opening the door for treatment of large surface area burns.[17,45] With this discovery, many patients have been treated with cultured epidermal autografts for burns and ulcerative conditions[46,47] allowing for permanent skin coverage in these tough-to-treat wounds.[17] Cultured epithelial autografts are commercially available as Epicel (Genzyme Tissue Repair Corp, Cambridge, Massachusetts). Epicel is indicated for use in deep dermal or full-thickness burns covering more than 30 percent body surface area. Epicel can be used alone or in conjunction with split-thickness autografts.[17] The formation of a dermal layer takes years to occur; therefore, Epicel is often used with dermal substitutes.[11,12]

Cultured autologous epithelial substitutes can also be found in the form of a suspension, such as Cell Spray (Avita Medical, Woburn, Massachusetts). The aerosolized route of application is simpler and allows for complete coverage of contoured wounds. The autologous suspensions require a split-thickness donor biopsy to harvest keratinocytes in the suspension, which takes approximately five days. The suspension then can be placed in the wound and an epidermal cover is created. It optimizes healing and scar quality.[17,48–50]

Another product is Hyalograft 3D (Fidia Advanced Biopolymers, Abano Terme, Italy). Unlike Epicel and Cell Spray, Hyalograft 3D is an autologous dermal substitute. Autologous cultured fibroblasts are seeded onto a three-dimensional hyaluronic acid derived scaffold.[17] A study by Caravaggi[51] demonstrated improved healing rates of dorsal diabetic foot ulcers with Hyalograft and Laserskin (Advanced Biopolymers, Abano Terme, Italy), which is another autologous epidermal substitute. This study found that pressure offloading appears to be a more important factor in healing for neuropathic plantar foot ulcers, but recommended that clinicians should consider autologous grafts when a total offloading cast is not recommended.[12,51]

The application of many of these autografts in post-surgical and other dermatological wounds is currently limited. However, necessary investigative research is on-going.[12,19,52–54] The disadvantages of epithelial autografts, such as Epicel, include product fragility and susceptibility to infection. Additionally, the culturing process takes several weeks, which can be inconvenient in clinical practice. The high cost, much more than the previously mentioned skin substitutes, and its short shelf-life, cause it

to be an impractical tool for a dermatologist.[12]

Skin substitutes are an important player in management of various wound etiologies. These products all aim to augment wound healing and closure, either temporarily or for a more permanent solution, depending on each substitute's composition. The various skin substitutes highlighted all offer distinct advantages yet come with certain disadvantages. The ultimate agent would be able to resist infection, lack antigenicity, be cost effective, widely available, durable, stable, prevent water loss, and provide coverage for every wound's unique characteristics, including the wound location, depth, underlying etiology, and susceptibility to infection.[20] No such substitute exists to date. A frontier of opportunity for advancement in this discipline therefore exists. Further testing of both biological and synthetic materials is required, along with more research of the existing skin substitutes currently in the market.

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